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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing: 14 January 1999 (14.01.99)	
International application No.: PCT/IB98/00933	Applicant's or agent's file reference: PC9835/76494
International filing date: 15 June 1998 (15.06.98)	Priority date: 01 July 1997 (01.07.97)
Applicant: FRIESEN, Dwayne, Thomas et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

22 September 1998 (22.09.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

TENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
PC9835/76494		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 98/ 00933	15/06/1998	01/07/1997
Applicant		
PFIZER PRODUCTS INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 98/00933

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/135 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 415 612 A (PFIZER INC.) 6 March 1991 see page 3, line 11 - page 4, line 10	1-29
P,X	WO 97 37640 A (ALZA CORPORATION) 16 October 1997 see examples 1-4,10-12	1-29
X	US 4 803 076 A (PFIZER INC.) 7 February 1989 see example 5	1-8,10, 12,13, 15-17, 19,20, 22-26, 28,29

[ ] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 August 1998	11/08/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Economou, D

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 98/00933

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0415612 A	06-03-1991	AU 617622 B	28-11-1991
		AU 6194390 A	18-04-1991
		CA 2024181 A,C	01-03-1991
		DE 69004529 D	16-12-1993
		DE 69004529 T	24-02-1994
		DK 415612 T	13-12-1993
		IE 63137 B	22-03-1995
		IL 95472 A	14-05-1996
		JP 3093719 A	18-04-1991
		NZ 235100 A	26-05-1997
		PT 95118 A,B	22-05-1991
		US 5130338 A	14-07-1992
WO 9737640 A	16-10-1997	AU 2337897 A	29-10-1997
US 4803076 A	07-02-1989	AU 582309 B	16-03-1989
		AU 7790587 A	10-03-1988
		CA 1310242 A	17-11-1992
		CN 1007700 B	25-04-1990
		DK 459187 A	05-03-1988
		EG 18717 A	30-11-1994
		EP 0259113 A	09-03-1988
		FI 873822 A,B,	05-03-1988
		HU 210491 B	28-04-1995
		IE 59939 B	04-05-1994
		JP 1893213 C	26-12-1994
		JP 6021058 B	23-03-1994
		JP 63063610 A	22-03-1988
		MX 165370 B	06-11-1992
		NO 174835 B	11-04-1994
		PT 85640 B	29-10-1993

EL 09/380825 — 0500

REC'D 09 NOV 1999
WIPO PCT

PATENT COOPERATION TREATY

1664 PCT
1615

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PC9835/76494		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB98/00933	15/06/1998	01/07/1997
International Patent Classification (IPC) or national classification and IPC A61K31/135		
Applicant PFIZER PRODUCTS INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/09/1998	05. 11. 99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Economou, D Telephone No. +49 89 2399 8599

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB98/00933

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-26 as originally filed

Claims, No.:

1-29 as received on 05/07/1999 with letter of 02/07/1999

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 22-29.

because:

☒ the said international application, or the said claims Nos. 22-29 (see separate sheet, item 1) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6,12,19 (see separate sheet, item 3)
	No:	Claims	1-5,7-11,13-18,20-21 (see separate sheet, item 3)
Inventive step (IS)	Yes:	Claims	6,12,19 (see separate sheet, item 3)
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-21 (see separate sheet, item 2a) 22-29 (see separate sheet, item 2b)
	No:	Claims	

2. Citations and explanations

see separate sheet

1). As far as the method disclosed in claims 22-29 can be practised on/in the human/animal body (see claim 24: "GI-tract") the subject-matter of the said claims (22-29) relates to a method of treatment of the human/animal body.

2). a). The subject-matter of claims 1-21 fulfils the requirements of industrial applicability.

b). For the assessment of the present claims 22-29 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3). Compositions comprising sertraline and solubilizing agents (or agents which according to the invention can be used as solubilizing agents) are known from **D1**(=US-A-4 803 076; see example 5) which discloses tablets comprising sertraline HCl and magnesium stearate (an organic acid salt which according to claim 7 of the present application can be used as a solubilizing agent) and from **D2** (=EP-A-0 415 612; see from page 3, line 11 to page 4, line 6) which discloses sertraline formulations comprising a plurality of compounds (magnesium stearate, sodium lauryl sulfate, sesame or peanut oil) which according to the present application (see claims 7, 9,13,14,20 and 21) can be used as solubilizing agents. Applicants argued in their letter dated 02.07.1999 that magnesium stearate does not fall within the scope of the present application due to its poor solubility. However, there is no mention in the application as originally filed that the solubilising agents must have a particular solubility. Hence, the objections raised in the communication dated 10.03.1999 are still maintained as regards novelty of claims 1-5, 7-11, 13-18 and 20-21. The same applies also due to the presence of sodium lauryl sulfate, sesame or peanut oil in the compositions, which were not excluded from the subject-matter as claimed. The fact that the above-mentioned compounds are not explicitly disclosed as solubilizing agents does not establish novelty of the claims since this property is an inherent property.

The subject-matter of claims 6,12 and 19 which is formally novel involves also an inventive step, since the problem which the present application solves, was not obvious from the prior art.

CLAIMS

1. A composition of matter comprising sertraline or a pharmaceutically acceptable salt thereof and an amount of a solubilizing agent sufficient to produce a concentration of dissolved sertraline in a use environment containing chloride ions which is 1.5 times higher than the concentration effected by a comparative composition of matter identical thereto but for the inclusion of said solubilizing agent, provided said solubilizing agent is not alginic acid, sodium citrate, calcium carbonate, or a polyethylene glycol having a molecular weight greater than 3350.

2. A composition of matter as defined in claim 1, wherein said use environment is the GI tract.

3. A composition of matter as defined in claim 1, wherein said use environment is an aqueous chloride ion-containing test medium.

4. A composition of matter as defined in claim 3, wherein said use environment is 0.075 M sodium chloride.

5. A composition of matter as defined in claim 1, which is an immediate release dosage form.

6. A composition of matter as defined in claim 1, which is a controlled release dosage form.

7. A composition of matter as defined in claim 1, wherein said solubilizing agent is selected from:

1) organic acids and organic acid salts;
2) partial glycerides;
3) glycerides;
4) glyceride derivatives;
5) polyethylene glycol esters;
6) polypropylene glycol esters;
7) polyhydric alcohol esters;
8) polyoxyethylene ethers;

9) sorbitan esters;

10) polyoxyethylene sorbitan esters; and

11) carbonate salts.

8. A composition of matter as defined in claim 4, wherein the amount of said solubilizing agent is sufficient to maintain, for at least 2 hours, the concentration of dissolved sertraline at a level which is at least 1.5 times higher than the concentration of sertraline produced by a comparative composition of matter identical thereto but for the inclusion of said solubilizing agent.

9. A composition as defined in claim 1, wherein said solubilizing agent is selected from aspartic acid, glyceryl monocaprylate, glyceryl monolaurate, calcium acetate, ascorbic acid, citric acid, and glutamic acid.

10. A composition of matter comprising sertraline or a pharmaceutically acceptable salt thereof and an amount of a solubilizing agent sufficient to produce and to maintain, for at least 2 hours in 0.075M sodium chloride, a concentration of dissolved sertraline which is at least 1.5 times higher than the concentration effected by a comparative composition of matter identical thereto but for the inclusion of said solubilizing agent, provided said solubilizing agent is not alginic acid, sodium citrate, calcium carbonate, or a polyethylene glycol having a molecular weight greater than 3350.

11. A composition of matter as defined in claim 10, which is an immediate release dosage form.

12. A composition of matter as defined in claim 10, which is a controlled release dosage form.

13. A composition of matter as defined in claim 10, wherein said solubilizing agent is selected from:

1) organic acids and organic acid salts;

2) partial glycerides;

3) glycerides;

4) glyceride derivatives;
5) polyethylene glycol esters;
6) polypropylene glycol esters;
7) polyhydric alcohol esters;
8) polyoxyethylene ethers;
9) sorbitan esters;
10) polyoxyethylene sorbitan esters; and
11) carbonate salts.

14. A composition as defined in claim 10, wherein said solubilizing agent is selected from aspartic acid, glyceryl monocaprylate, glyceryl monolaurate, calcium acetate, ascorbic acid, citric acid, and glutamic acid.

15. A composition of matter comprising sertraline or a pharmaceutically acceptable salt thereof and an amount of a solubilizing agent sufficient to effect, *in vivo,* a C_{max} and/or an AUC which is greater by at least 10% than the C_{max} and/or AUC effected by a comparative composition of matter identical thereto but for the inclusion of said solubilizing agent, provided said solubilizing agent is not alginic acid, sodium citrate, calcium carbonate, or a polyethylene glycol having a molecular weight greater than 3350.

16. A composition as defined in claim 15, wherein said C_{max} and/or AUC effected by said solubilizing agent-containing composition is at least 15% higher than the corresponding C_{max} and/or AUC effected by said comparative composition.

17. A composition as defined in claim 16, wherein said C_{max} and/or AUC effected by said solubilizing agent-containing composition is at least 20% higher than the corresponding C_{max} and/or AUC effected by said comparative composition.

18. A composition of matter as defined in claim 15, which is an immediate release dosage form.

19. A composition of matter as defined in claim 15, which is a controlled release dosage form.

20. A composition of matter as defined in claim 15, wherein said solubilizing agent is selected from:

1) organic acids and organic acid salts;
2) partial glycerides;
3) glycerides;
4) glyceride derivatives;
5) polyethylene glycol esters;
6) polypropylene glycol esters;
7) polyhydric alcohol esters;
8) polyoxyethylene ethers;
9) sorbitan esters;
10) polyoxyethylene sorbitan esters;
11) carbonate salts.

21. A composition of matter as defined in claim 15, wherein said solubilizing agent is selected from aspartic acid, glyceryl monocaprylate, glyceryl monolaurate, calcium acetate, ascorbic acid, citric acid, and glutamic acid.

22. A method of increasing the solubility of sertraline in an aqueous chloride ion-containing use environment, comprising administering said sertraline to said use environment in a composition of matter additionally comprising a solubilizing agent, provided said solubilizing agent is not alginic acid, sodium citrate, calcium carbonate, or a polyethylene glycol having a molecular weight greater than 3350.

23. A method as defined in claim 22, wherein the concentration of dissolved sertraline in said use environment also containing said solubilizer is at least 1.5-fold higher than the concentration of sertraline effected by a comparative composition identical to said solubilizing agent-containing composition except for the inclusion of said solubilizing agent.

24. A method as defined in claim 22, wherein said use environment is the GI tract.

25. A method as defined in claim 22, wherein said use environment is an aqueous chloride ion-containing test medium.

26. A method as defined in claim 25, wherein said medium is 0.075 M sodium chloride.

27. A method as defined in claim 22, wherein said composition of matter is in the form of an immediate release dosage form.

28. A method as defined in claim 22, wherein said composition of matter is in the form of a controlled release dosage form.

29. A method as defined in claim 22, wherein said solubilizing agent is selected from:

1) organic acids and organic acid salts;
2) partial glycerides;
3) glycerides;
4) glyceride derivatives;
5) polyethylene glycol esters;
6) polypropylene glycol esters;
7) polyhydric alcohol esters;
8) polyoxyethylene ethers;
9) sorbitan esters; and
10) polyoxyethylene sorbitan esters.
11) carbonate salts

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

09/380 825 5000

Applicant's or agent's file reference NAE19960899PC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP98/01256	International filing date (*day/month/year*) 05 March 1998 (05.03.1998)	Priority date (*day/month/year*) 07 March 1997 (07.03.1997)
International Patent Classification (IPC) or national classification and IPC C07C 51/48		
Applicant BASF AKTIENGESELLSCHAFT		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01 October 1998 (01.10.1998)	01 June 1999 (01.06.1999)
Name and mailing address of the IPEA/EP European Patent Office D-80298 Munich, Germany Facsimile No. 49-89-2399-4465	Authorized officer Telephone No. 49-89-2399-0

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

ernational application No.
PCT/EP98/01256

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-7,9,10,12,13, as originally filed,
pages _____, filed with the demand,
pages 8,11, filed with the letter of 20 April 1999 (20.04.1999),
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-9, filed with the letter of 20 April 1999 (20.04.1999),
Nos. _____, filed with the letter of _____.

☐ the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-9	YES
	Claims		NO
Inventive step (IS)	Claims	1-9	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims		NO

2. Citations and explanations

This report cites the following documents:

D1 DE-A-21 61 525

D2 JP-A-48 039 421

Amendments - Article 34(2)(b)

Amendments filed with the letter of April 20, 1999:

- Inclusion of additional features in Claim 1:
  - alkanes, alkanols, alkenes or alkenals, with C_3 or C_4 atoms or the methyl ether of tert-butanol, were added to the definition of the extraction agent in line with the description (page 4, lines 15-19 and 20-21).
  - the feature of dependent Claim 5 was included in Claim 1 (page 5, lines 22-23).

- Agreement between the description and the claim:
  - description (page 8, line 5) with Claim 6 (page 15, line 6)
  - description (page 8, line 13) with Claim 8 (page 15, line 14)

- Corrections (PCT Rule 91.1(b))
  - the dwelling time for the phase separation lasts 3 minutes (Example 1, page 11, line 9)
  - the use of "methacrylic acid" in Example 1 (page 11) in line with the definition in the description (page 1, lines 19-20).

The above corrections do not represent extensions of the subject matter of the international application as filed and therefore meet the criterion stipulated in PCT Article 34(2)(b)).

Novelty - PCT Article 33(2)

1. **D1** discloses a method for extracting (meth)acrylic acid from solutions containing these compounds using selective solvents (methyl ethyl ketone and benzene; page 3, lines 13-17).

   D2 discloses a method for obtaining purer (meth)acrylic acid through extraction using a mixture of methyl ethyl ketone and diisobutylene.

   The extraction agent solutions in the two aforementioned cases, like the individual components themselves, cannot be used in the (meth)acrylic acid synthesis (feature c) of Claim 1 of the invention. The subject matter of Claim 1 is therefore novel over **D1** or **D2**.

1.1 For the same reasons as above, the subject matter of dependent Claims 2-9 is also novel.

Inventive step - PCT Article 33(3)

2. **D1** discloses a method for extracting (meth)acrylic acid using methyl ethyl ketone and benzene (page 3, lines 13-17).

2.2 The invention addresses the problem of preparing a different method for extracting an aqueous solution containing (meth)acrylic acid, which uses an adjuvant-free solution and requires only minimal expenditure on technical appliances.

2.3 As a solution, the present invention concerns a method for extracting an aqueous solution containing (meth)acrylic acid by bringing the aqueous solution into contact with a solution containing at least one extraction agent which can be converted into (meth)acrylic acid and forms a miscibility gap with the aqueous solution to produce an organic phase containing the (meth)acrylic acid and the extraction agent, and an aqueous phase.

2.4 The extraction agent mixture known from **D1** is advantageous in that the distribution coefficient thereof is greater than that of the pure extraction agent methyl ethyl ketone and benzene (page 5, paragraph 1). Since neither the mixture nor the individual components can be used as an educt in the (meth)acrylic acid synthesis, additional costs, i.e. on technical appliances, are incurred for the recovery of the extraction agent. In contrast, the claimed extraction agent solution can be used to recover (meth)acrylic acid without this recovery stage. This possibility was disclosed in neither **D1** nor

D2. Consequently, the invention is non-obvious. The subject matter of Claim 1 involves an inventive step.

2.5 For the same reasons as above, an inventive step can be acknowledged for the subject matter of dependent Claims 2-9.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. Contrary to PCT Rule 5.1(a)(ii), the description does not cite document **D1** nor the relevant prior art disclosed therein.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/135, 9/20 — A1

(11) International Publication Number: **WO 99/01120**

(43) International Publication Date: 14 January 1999 (14.01.99)

(21) International Application Number: PCT/IB98/00933

(22) International Filing Date: 15 June 1998 (15.06.98)

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(54) Title: SOLUBILIZED SERTRALINE COMPOSITIONS

(57) Abstract

Compositions of matter comprising sertraline and a solubilizing agent which increases the solubility of sertraline in aqueous chloride ion-containing use environments.

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Solubilized Sertraline Compositions

Field of the Invention

This invention relates to a composition comprising sertraline or a pharmaceutically acceptable salt thereof and a solubilizing agent which prevents gel formation or otherwise maintains the solubility of sertraline in a use environment containing chloride ions. The invention further relates to a method of treating a psychiatric or other illness comprising administering sertraline in such a solubilized composition to a mammal, including a human patient, in need of such treatment.

Background of the Invention

Sertraline is a selective serotonin reuptake inhibitor (SSRI), which is useful as an antidepressant and anorectic agent, and in the treatment of obsessive-compulsive disorder, premenstrual dysphoric disorder, post-traumatic stress disorder, chemical dependencies, anxiety-related disorders, panic and premature ejaculation.

Sertraline is most commonly prescribed for therapy of depressive illness, in the general dose range 50-200 mg/day. Sertraline has an elimination half-life of 23 hr and is dosed once daily. Commercially, sertraline is available as the hydrochloride salt which is undeniably therapeutically effective, many patients having availed themselves of the benefits of this drug.

Some forms of sertraline, particularly salts which exhibit high solubility, can be problematic, however. Such salts, generally those having an aqueous solubility in excess of 10 mg/mL, can exhibit a tendency to form a gel and/or exhibit reduced solubility (e.g., precipitate as a salt or as the free base having a lower solubility in the environment of use than the salt form originally administered) when exposed to a use environment containing chloride ions such as the gastrointestinal tract. The gel itself tends to dissolve slowly and otherwise releases sertraline at a slow rate, thereby affecting absorption. It is not known whether gelation is the only mechanism which impacts the solubility of sertraline in a use environment. However, therapeutic difficulties can accordingly arise from administering an immediate-release dosage form *in vivo* if solubility is affected, regardless of mechanism. Problems can similarly arise in the case of controlled-release dosage forms since the controlled release profile of the dosage form can be altered *in vivo* by factors affecting solubility. The

unanticipated phenomenon of gelation of sertraline salts in a chloride ion-containing environment can thus create therapeutic difficulties by unexpectedly altering the release profile of a dosage form, whether immediate-release or controlled-release. The mechanism of sertraline gelation is not well understood, and can be all the more problematic therapeutically since the release characteristics of a gel formed *in situ* may not be anticipated.

In particular, gelling of sertraline in sustained-release dosage forms can be detrimental in those sustained release systems known as non-eroding matrix systems, reservoir systems, and osmotic systems. In each of these types of sustained release formulations release of the drug is dependent on transport of the drug across a distance within the device (matrix or coating layer) to the surrounding fluid. This drug transport can occur by diffusive or convective mechanisms. In both mechanisms, formation of a gel can reduce transport by an order of magnitude or more and in some cases can result in devices that exhibit incomplete drug release (e.g., less than 70% of the total drug in the formulation).

Summary Of The Invention

This invention provides a composition of matter, suitable for administration to a mammal, including a human, comprising sertraline or a pharmaceutically acceptable salt thereof and an amount of an excipient, herein termed a "solubilizing agent" sufficient to effect a concentration of dissolved sertraline in a use environment containing chloride ions which is at least 1.5 times higher, preferably 2 times higher, more preferably 3 times higher than the concentration effected by a comparative composition of matter (i.e., a control) identical thereto but for the inclusion of said solubilizing agent. The use environments mainly intended are the aqueous *in vivo* digestive fluids of the gastrointestinal (GI) tract including the stomach, small intestine and large intestine, and aqueous *in vitro* chloride ion-containing test media, as further described below. The compositions are suitable for formulating into oral dosage forms including tablets, capsules, multiparticulates, powders for oral suspension, and unit dose packets (sometimes referred to in the art as a "sachet"). In addition the compositions can be used in liquid dosage forms such as oral solutions or suspensions and injectable formulations. For making the compositions of this invention into oral dosage forms, conventional techniques known to the art can be

employed. Th composition can additionally comprise other conventional pharmaceutical ingredients and/or a pharmaceutically acceptable carrier.

By this invention, it has been determined that in cases of dosage forms containing sertraline salts which form gels or which otherwise exhibit reduced solubility in a use environment, solubility may advantageously be increased, and in some cases solution viscosity may be advantageously decreased, by employing the sertraline salt together with a solubilizing agent which increases the sertraline's solubility. The solubilizing agent preferably also maintains solubility, meaning that the level of dissolved sertraline in a use environment, regardless of the salt employed, is held at a concentration greater than or equal to 1.5 times the concentration of sertraline in a like formulation without solubilizing excipient, for at least 2 hours. For many dosage forms it may be advantageous to maintain the sertraline concentration greater than or equal to 1.5 times the concentration of sertraline in like formulations without solubilizing excipient for longer periods of time such as 4 hours, 8 hours, 16 hours, or 20 hours, and this can be effected by the choice and amount of solubilizing agent. It has otherwise been determined that in a chloride ion-containing use environment without a solubilizing agent, for example a test environment such as 0.075M sodium chloride solution, sertraline solubility is generally less than 10 mgA/mL, usually less than 5 mgA/mL, regardless of the salt employed, and despite the fact that many of the salts themselves exhibit solubilities in pure water (i.e., no chloride ions) well in excess of 10 mgA/mL. Solubilizing agents thus could also be construed to be compounds that maintain sertraline concentrations of 10mgA/ml or greater in chloride-ion-containing environments of use.

Reference herein to "a solubilizing agent" herein, including the claims, shall be understood as also including the use of more than one solubizing agent in a composition, added separately or as a mixture.

As mentioned above, the term "use environment" can refer to the aqueous *in vivo* chloride ion-containing digestive fluids of the stomach, or to an *in vitro* chloride ion-containing aqueous environment used to test a dosage form for its sertraline release characteristics. A useful *in vitro* test environment for purposes of this invention is 0.075M sodium chloride. 0.075M sodium chloride is preferred as a test medium because of its ready availability and similar chloride ion concentration to the

low r levels of chloride ions found in th fluids in the GI tract. Blood & Other Body Fluids, Dorothy S. Dittmer, ed., Federation of American Societies for Experimental Biology, Washington, D.C., 1961, pp. 404-419. Thus, as an additional feature, this invention provides an *in vitro* test to determine whether a dosage form is within the scope of the invention. That is, the invention provides a composition of matter comprising sertraline or a pharmaceutically acceptable salt thereof and an amount of a solubilizing agent sufficient to produce and to maintain, for at least 2 hours in 0.075M sodium chloride, a concentration of dissolved sertraline which is at least 1.5 times higher than the concentration effected by a comparative composition of matter identical thereto but for the inclusion of said solubilizing agent. Agitation should be employed during the test although, as explained below, the degree or type of agitation is not critical. Salt solution temperature is not believed to be particularly critical so long as it is about 37°C, plus or minus 3°C, throughout the test. Excipients, including the solubilizing agent(s) should be at the desired concentration in the aqueous test solution prior to adding sertraline and sodium chloride. Sertraline is then added to a concentration ranging between 80% to 100% of its saturation concentration in the test solution. This solution should be decanted off or filtered away from any solids. To this solution a 3M NaCl solution is slowly added with stirring until the NaCl concentration in the test solution is 0.075M. The sertraline concentration in this test solution after 2 hours is compared with a control solution made in the same manner and consisting of the same components except the solubilizing agent.

Alternatively, a solubilizing excipient can be identified in an *in vivo* test such as a crossover study. In an *in vivo* crossover study a solubilized sertraline-containing dosage form is dosed to half a group of 12 or more humans and, after an appropriate washout period (e.g., one week) the same subjects are dosed with a dosage form otherwise identical but for inclusion of the solubilizing agent. The other half of the group is dosed with the non-solubilized dosage form first, followed by the solubilized dosage form. Maximum concentration in the blood (C_{max}) and/or bioavailability, measured as the area under the curve (AUC) for a plot of the concentration of sertraline in blood versus time, is determined for each group. By comparison, assessment of the solubilized dosage form can be made. If the average

C_{max} or AUC for the formulation containing the solubilizing agent is greater by 10% or more than the formulation without the solubilizing agent, then the solubilizing excipient is an embodiment of this invention. It is preferred that the C_{max} and/or AUC be greater by at least 15%, and more preferred either or both be greater by at least 20%. The determination of AUC's is a well known procedure and is described, for example, in "Pharmacokinetics; Processes and Mathematics," by Peter Welling (ACS Monograph 185, Amer. Chem. Soc., Wash. D. C., 1986). Thus, as an additional feature of the invention, the invention provides a composition of matter comprising sertraline or a pharmaceutically acceptable salt thereofand an amount of a solubilizing agent sufficient to effect, *in vivo,* a C_{max} and/or an AUC which is greater by at least 10% than the C_{max} and/or AUC effected by a comarison composition of matter (i.e., a control) identical thereto but for the inclusion of said solubilizing agent.

The invention further provides a method of increasing the solubility of sertraline in an aqueous chloride ion-containing environment, comprising administering said sertraline in a composition of matter comprising sertraline and a solubilizing agent.

The invention is surprising in that, prior to the invention, it was not known that (1) the phenomenon of reduced sertraline solubility in chloride ion-containing environments existed, nor that (2) any chemical agent existed which would reduce or prevent sertraline gelation or reduced sertraline solubility in chloride ion-containing use environments or otherwise operate to increase sertraline's solubility in such use environments. The term "solubilized sertraline" is used herein to refer to a composition comprising sertraline or a sertraline salt plus an excipient (i.e. the solubilizing agent) which prevents gelation or otherwise increases, and preferably maintains, the solubility of the sertraline salt in an *in vivo* or *in vitro* chloride ion-containing use environment. Likewise, the term "solubilize" is used to denote that the solubility of a sertraline salt is being increased by at least 1.5 times in a use environment over what it would be in the absence of a solubilizing agent.

The invention is preferred for use with the aspartate, acetate, and lactate salts which are salts that exhibit high solubilities in water relative to the free base. These salts are disclosed in commonly assigned co-pending application PC9337JTJ, filed

as a PCT application designating the United States, and herein incorporated by reference.

For convenience and consistency, reference to "sertraline" in terms of therapeutic amounts herein, including the claims, is to active sertraline, abbreviated herein as "mgA", i.e., the non-salt, non-hydrated free base having a molecular weight of 306.2. Amounts in mgA can conveniently be converted to equivalent weights for whatever salt form is desired.

Many solubilizing agents useful herein can be grouped into several broad categories:

1. Organic acids and organic acid salts;
2. Partial Glycerides, i.e., less than fully esterified derivatives of glycerin, including monoglycerides and diglycerides;
3. Glycerides;
4. Glyceride derivatives;
5. Polyethylene glycol esters;
6. Polypropylene glycol esters;
7. Polyhydric alcohol esters;
8. Polyoxyethylene ethers;
9. Sorbitan esters; and
10. Polyoxyethylene sorbitan esters.
11. Carbonate salts

Detailed Description

The amount of solubilizing agent employed in a composition according to the invention depends on the particular solubilizing agent employed.

In the case of solubilizing agents which are organic acids the preferred amount of solubilizer can be calculated as a ratio multiplied by the quantity of sertraline to be used, wherein the ratio is of organic acid solubility to solubility of sertraline salt:

(organic acid or salt solubility/sertraline or sertraline salt solubility) x quantity of sertraline

where the solubilities referred to are in mg/ml. The above expression is approximate, and some adjustment may be advantageous for optimization. Generally the above expression will give a quantity which is plus or minus 25% of the final value employed, although higher quantities of solubilizing agent can be incorporated without any particular additional advantage. In addition, organic acid salts can be added to modify the pH and/or solubility of the organic acid, effectively optimizing the solubilization effect of the agents.

For other types of solubilizing agents listed, typically the amount of solubilizing agent employed in the dosage form will be 1 to 150% by weight of the amount of sertraline employed therein, preferably 1 to 100%, more preferably 3 to 75%. Amounts of solubilizing agent higher than 150% may be employed, although it is believed that in most cases no particular advantage would be provided.

Salts of sertraline or excipients that in combination with sertraline aid in solubilizing sertraline can be beneficial to virtually any type of sertraline dosage forms intended for oral administration, including immediate release as well as controlled release systems, including (1) sustained-release dosage forms which meter out sertraline as they progress through the gastrointestinal system and (2) delayed release systems which release sertraline after an initial delay period following ingestion. Immediate-release systems are well known and commercially available in both solid and liquid formulations. Controlled release dosage forms of sertraline are discussed and disclosed in commonly assigned co-pending applications Pfizer Docket PC9337JTJ and PC9824JTJ, each of which is a PCT application designating the United States and each herein incorporated by reference in its entirety. Solubilized sertraline can enhance release from the dosage form by increasing the concentration gradient for diffusive based systems such as matrix dosage forms and reservoir dosage forms. Solubilized sertraline can also enhance delivery from osmotic dosage forms in that a more soluble sertraline can increase the osmotic pressure in the core and increase the sertraline concentration in the fluid that is pumped or extruded out of the dosage form. In addition, solubilized sertraline can benefit sustained-release formulations by aiding absorption of drug from the G.I.

tract. For xampl , high r concentrations of drug in the colon can increase absorption due to a higher concentration gradient across the intestinal wall.

It is noted that currently available commercial dosage forms of sertraline are immediate-release dosage forms containing sertraline hydrochloride. Even though the hydrochloride has proven to be very effective, it is possible that dosage forms containing the hydrochloride can also benefit by the addition of a solubilizing agent.

Examples of organic acids useful in the invention include malic, citric, erythorbic, adipic, glutamic, aspartic, maleic, aconitic, and ascorbic acid. Preferred acids are citric, erythorbic, ascorbic, glutamic, and aspartic. Salts of organic acids such as alkalkine earth metal (magnesium, calcium) salts and alkali metal (lithium, potassium, sodium) salts are also effective as well as mixtures of organic acids and their salts. Calcium salts such as calcium carbonate, calcium acetate, calcium ascorbate, calcium citrate, calcium gluconate monohydrate, calcium lactobionate, calcium gluceptate, calcium levulinate, calcium pantothenate, calcium proprionate, calcium phosphate dibasic, and calcium saccharate are preferred organic acid salts.

Examples of compounds within the other categories mentioned above are summarized in Table 1.

Table 1

Solubilizing Agents

Class	Examples, Chemical Name	Examples, Trade Designation, (Vendor)
Partial Glycerides	Glyceryl Monocaprylate	Monocaprylin® (Sigma), Capmul® MCM(Abitec), Imwitor® 308 (Hüls)
	C8-C10 Partial Glycerides	Capmul® MCM (Abitec), Imwitor® 742 (Hüls), Imwitor® 988 (Hüls)
	Glyceryl Monooleate	Myverol® 18-99 (Eastman), Calgene® GMO (Calgene), Capmul® GMO(Abitec)
	Glyceryl Monolinoleate	Myverol® 18-92 (Eastman)
	Glyceryl Monostearate	Imwitor® 191 (Hüls) Calgene® GSO(Calgene)
	Glycery Monolaurate	Imwitor® 312 (Hüls) Calgene® GLO (Calgene)
	Glyceryl Dilaurate	Capmul® GDL (Abitec)
Glycerides	Triacetin	Triacetin (Sigma)
Glyceride Derivatives	PEG-Derivitized Glycerides	Cremophor® RH40, Cremophor® RH60 (BASF), Acconon CA5, CA-9, CA-15, W230, TGH (Abitec)
	Polyglycolized Glycerides	Gelucire® 44/14, 42/12, 50/13, 53/10, 35/10, 48/09, 46/07, 62/05, 50/02; Labrasol® (Gattefosse); Capmul® 3GO; 3GS, 6G2O, 6G2S, 10G4O, 10G10O (Abitec)
Polyethylene glycol Esters	PEG 200 Monolaurate, PEG 400 Monolaurate, PEG 600 Monolaurate	Calgene® 20-L, Calgene® 40-L, Calgene® 60-L
	PEG 200 Monostearate, PEG 400 Monostearate, PEG 600 Monostearate	Calgene® 20-S, Calgene® 40-S, Calgene® 60-S
	PEG 200 Dilaurate, PEG 400 Dilaurate, PEG 600 Dilaurate	Calgene® 22-L, Calgene® 42-L Calgene® 62-L
Polypropylene Glycol Esters	Propylene Glycol Dicaprylate	Captex® 200 (Abitec)
Polyhydric Alcohol Esters	Diethylene Glycol Monolaurate	Calgene® DGL

	Propylene Glycol Monolaurate	Calgene® PGML
	Ascorbyl Palmitate	Ascorbyl Palmitate (Sigma)
Polyoxyethylene Ethers	PEG Lauryl Ether	Nonionic L-4 (Calgene)
	PEG Stearyl Ether	Nonionic S-20 (Calgene), Myrj 45, 52, 53, 59 (Sigma)
Sorbitan Esters	Sorbitan Monolaurate	Calgene® SML, Span® 20 (Sigma)
	Sorbitan Monooleate	Calgene® SMO, Span® 80 (Sigma)
Polyoxyethylene Sorbitan Esters	POE-20 Sorbitan Monolaurate	Calgene® PSML-20, Span® 20(Sigma), Tween 20 (Sigma), Capmul® POE-L (Abitec)
	POE-20 Monooleate	Tween® 80, PSMO-20
Saccharide Esters	Sucrose Monolaurate	Ryoto LW-1540 (Chem Service)
Phospholipids	Phosphatidyl choline	Lecithin (Sigma)
	Mixed phospholipids	Emphos D70-30C (Witco)
Block Co-polymers	PEO-PPO Block Copolymers	Pluronic® F-68, F127, L-62 (BASF)
Polyethylene Glycols	PEG 3350	Various sources

In addition other compounds useful as solubilizing agents in the invention are ethyl propionate, methyl paraben, propyl paraben, propyl gallate, niacinamide, ethyl vanillin, paraaminobenzoic acid, butylated hydroxyanisole, imidurea, and glycine. It is also noted that preferred compositions include mixtures of an organic acid with or without a corresponding organic acid salt, and one or more of the non-organic solubilizers listed above or in Table 1. It is also noted that it has generally been observed that in order to be most effective the solubilizer should have a solubility in the aqueous chloride-ion containing use environment of at least 1mg/ml, and preferably greater than 5mg/ml.

A preferred group of solubilizing agents, in addition to the preferred organic acids previously mentioned, includes those in Table 2.

Table 2

Preferred Solubilizing Agents

Class	Examples, Chemical Name	Examples, Trade Names (source)
Partial Glycerides	Glyceryl monocaprylate	Monocaprylin® (sigma), Capmul® MCM(Abitec), Imwitor® 308 (Hüls)
	C8-C10 Partial Glycerides	Capmul® MCM (Abitec), Imwitor® 742 (Hüls), Imwitor® 988 (Hüls)
	Glyceryl Monostearate	Imwitor® 191 (Hüls) Calgene® GSO(Calgene)
	Glyceryl Monolaurate	Imwitor® 312 (Hüls) Calgene® GLO (Calgene)
Glycerides	Triacetin	Triacetin® (Sigma)
Sorbitan Esters	Sorbitan Monolaurate	Calgene® SML, Span® 20 (Sigma)
	Sorbitan Monooleate	Calgene® SMO, Span® 80 (Sigma)
Phospholipids	Phosphatidyl choline	Lecithin® (Sigma)
	Mixed phospholipids	Emphos D70-30C (Witco)
Block Co-polymers	PEO-PPO Block Copolymers	Pluronic® F-68, F127, L-62 (BASF)
Polyethylene Glycols	PEG 3350	Various sources

Note: Commercial vendors shown above are as follows:

Abitec Corp. Janesville, WI

BASF, Parsippany, NJ

Calgene Chemical Inc. Skokie, IL

Chem Service, Inc., West Chester, PA

Hüls America, Piscataway, NJ

Sigma, St. Louis, MO

Witco, Houston, TX

Preferred combinations of solubilizing agents include (1) an organic acid plus a salt of the same or a different organic acid, (2) an organic acid plus a non-ionic solubilizing agent such as any of those listed in Table 1, and (3) an organic acid plus a salt of the same or a different organic acid plus a non-ionic solubilizing agent.

Particularly preferred individual solubilizing agents include aspartic acid, glyceryl monocaprylate, glyceryl monolaurate, calcium acetate, ascorbic acid, citric acid, glutamic acid, and calcium carbonate. Aspartic acid, glyceryl monocaprylate, glyceryl monolaurate and calcium acetate are most preferred.

As previously discussed, a dosage form can be tested *in vitro* to determine whether an excipient has a solubilizing effect on sertraline in a chloride-ion containing use environment and thus is useful as a solubilizing agent. A 0.075M NaCl solution is preferred for use as a test medium although other chloride-ion containing solutions with equivalent or higher chloride ion concentration than 0.075M (e.g., 0.1N HCl or isotonic saline) may be used to determine the solubilizing effect of a test excipient. In some cases reduced solubility is evident simply by adding a dosage form such as a powder to the test medium because gelation is visible. Similar problems may be evident in a dosage form such as a tablet if the tablet is, for example, cut open and gelation is visible on its open face. A recommended procedure is to initially make a solution containing the desired excipients, including solubilizing agent(s). The excipients can be at any concentration relevant to the intended dosage form, but are typically for organic acids and soluble salts or sugars 80-100% of saturation. For other surfactant-like compounds, concentrations typically range from 1 to 150% of the sertraline concentration in the test solution. Sertraline is added to this excipient-containing solution at a concentration typically 80-100% of saturation. The solution is filtered or decanted to remove any solids and then a 3M solution of sodium chloride is added until the sodium chloride concentration is 0.075M. The concentrated sodium chloride solution should be added dropwise with stirring. This test medium should be kept at a temperature on the order of 37°C for at least 2 hours at which time the sertraline concentration in solution is determined. It is preferred that the sertraline concentration be maintained for 4 hours, more preferably for 8 hours, still more preferably for 16 hours, and most preferably for at least 20 hours. The amount of agitation is not critical. When sampling the test medium, filtration or centrifugation

can be employed to obtain solution that is free of any solids or gel material, and also to avoid inclusion of particulates (which may contain sertraline) in the sample. Analysis of the samples to determine sertraline concentration can be accomplished via several conventional analytical methods, such as by high performance liquid chromatography (HPLC). For example, sertraline concentrations can be determined using reverse phase HPLC with a ULTRACARB® 5 ODS 4.6 x 250 mm column (Phenomonex, Torrance, CA), and a mixture of acetic acid, triethylamine, acetonitrile, and water as mobile phase, with UV detection at 230 nm. For example, the mobile phase can be prepared by combining, with stirring, 2.86 ml of glacial acetic acid, 3.48 ml of triethylamine, diluting to a liter with water, and filtering and degassing. Flow rates are typically on the order of 1.5 ml/min, and retention times about 4 minutes.

Dosage forms with solubilizing agent can be formulated by conventional techniques. Immediate release dosage forms can be capsules, tablets, multiparticulates, liquid solutions or suspensions. Capsule formulations can be either soft gelatin capsules where the sertraline is either dissolved or suspended within the capsule core or hard gelatin capsules filled with multiparticulates, tablets or a liquid (solution or suspension) fill. Immediate release tablets can be by techniques standard in the industry by simply including the solubilizing agent as one or more of the tablet excipients. Likewise immediate-release multiparticulates can be made that include solubilizing agents by techniques such as extension spheronization, rotary granulation, coating seed cores or other methods common in the pharmaceutical industry. Liquid formulations consisting of a solution or suspension or both can be made by methods common in the pharmaceutical industry.

Controlled-release dosage forms can also be made that include solubilizing agents by methods common in the pharmaceutical industry. Controlled release dosage forms include a wide variety of dosage forms that impart control over the dissolution rate or rate of release of sertraline from the dosage form. Such dosage forms include but are not limited to sustained release, delayed and then immediate release, delayed and then sustained release and a dosage form with a small portion of sertraline released immediately and then followed by the majority of the sertraline in the dosage release at a sustained rate. Other algorithms of release can also be

attained such as pulsitile release. Many such formulations are described in aforementioned co-pending applications PC9337JTJ and PC9824JTJ.

Standard techniques can be used to make controlled release dosage forms. For example, tablets can be made by commonly used direct compression methods that contain sertraline and a solubilizing agent. To provide delayed release, a pH-sensitive coating can be applied to these tablets via a side-vented pan coater (e.g., HCT-60 tablet coater, Vector Corp.). The pH sensitive coating is resistant to low pH environments such as typically in the stomach and then dissolves, releasing sertraline, in neutral pH environment such as typically in the small intestine. Such coating materials (e.g., cellulose acetate phthalate or methacrylic acid copolymer) are common in the pharmaceutical industry. Alternatively, the tablets can be coated with a porous or semipermeable membrane coating to provide sustained release of the tablet cores. A particularly useful process for applying a membrane coating comprises dissolving the coating polymer in a mixture of solvents chosen such that as the coating dries, a phase inversion takes place in the applied coating solution, resulting in a membrane with a porous structure. Numerous examples of this type of coating system are given in European Patent Specification 0 357 369 B1, published March 7, 1990, herein incorporated by reference. Many other types of controlled release dosage forms can also be made that benefit from the inclusion of solubilizing agents such as matrix systems which include but are not limited to 1) non-eroding matrices, tablets, multiparticulates and hydrogel-based systems; 2) hydrophilic eroding, dispersible or dissolvable matrix systems, tablets and multiparticulates; and 3) coated matrix systems. Another class of controlled-release dosage forms consists of reservoir systems where release of the drug is modulated by a membrane, such as capsules and coated tablets or multiparticulates. A third class consists of osmotic-based systems such as 1) coated bilayer tablets; 2) coated homogeneous tablet cores; 3) coated multiparticulates; and 4) osmotic capsules. A fourth class consists of swellable systems where drug is release by a swelling and then extrusion of the core components out through a passageway in a coating or surrounding shell or outer layer.

The invention is further illustrated by the following examples, which are not to be taken as limiting.

Example 1

This example illustrates that organic acids have the ability to raise the solubility of the hydrochloride salt of sertraline. The acids were tested by dissolving the candidate acid in water and then stirring excess sertraline hydrochloride in the acid solution for at least 8 hours. The concentration of sertraline in the supernatant was then measured by HPLC analysis. The results of this test are shown in Table 1-1, below. Most of the acids listed in the table successfully raised the solubility of sertraline hydrochloride (normal solubility 2.5 mg/ml).

Table 1-1

Excipient	Approximate Excipient Concentration (mg/ml)	Sertraline Solubility (mg/ml)
D,L-malic acid	900	21
Citric acid	600	20
Erythorbic acid	400	19
Adipic acid	14	12
Maleic acid	700	6.4
L-aspartic acid	10	5.5
Tartaric acid	1400	5.5
L-glutamic acid	12	5.4
Fumaric acid	11	3.1
Tannic acid	2000	2.8
D,L-tyrosine	600	2.2

Preferred acids, based on the above-described test, are malic, citric, erythorbic, and adipic acids. Maleic, L-aspartic, tartaric, and L-glutamic acids also significantly improved sertraline hydrochloride solubility. Some controlled-release dosage forms with such acids in the core will perform better than those without such acids. This is particularly true for osmotic-based formulations that deliver a solution of drug.

Example 2

This example illustrates that organic acids have the ability to raise the solubility of the acetate salt of sertraline by a test method similar to that used for the hydrochloride salt described in Example 1. The solubilizing agent, its concentration, and resulting sertraline solubility are shown in Table 2-1 below. Based on these results, preferred acids to include in a dosage form where increased sertraline

acetate solubility is desired are ascorbic, erythorbic, citric, lactic, aspartic, glutamic, and aconitic acids.

Table 2-1

Excipient	Excipient Concentration (mg/ml)	Sertraline Solubility (mg/ml)
Ascorbic acid	400	>425
Erythorbic acid	400	>330
Citric acid	600	146
Lactic acid	213	>294
Aspartic acid	7	110
Glutamic acid	12	108
Aconitic acid	500	>92
Itaconic acid	150	72
Succinic acid	77	28
None	–	64

Example 3

This example illustrates that organic acids and three calcium salts have the ability to raise the aqueous solubility of the lactate salt of sertraline using a method similar to that used for the hydrochloride salt described in Example 1. The solubilizing agent, its concentration in the aqueous test solution, and the sertraline lactate solubility in the test solution are listed in Table 3-1 below. Solubility of sertraline lactate in water is approximately 125 mg/ml. The data below show that eight organic acids effected sertraline lactate solubilities about the same as or higher than 125 mg/ml; adipic, erythorbic, itaconic, citric, aspartic, glutamic, histidine, and ascorbic. Also, a solution of a mixture of two of these acids also had high solubility; ascorbic and aspartic. Sertraline lactate solubility was also high in calcium salt solutions, either alone (calcium citrate) or mixed with ascorbic acid.

Table 3-1

Excipient	Excipient Concentration (mg/ml)	Sertraline Lactate Solubility (mg/ml)
Adipic acid	14	360
Erythorbic acid	400	>217
Itaconic acid	150	>202
Citric acid	600	162
Aspartic acid	7	>155
Glutamic acid	12	>125
Histidine	42	>116
Ascorbic/Aspartic	400/7	116
Ascorbic	400	102
Glycine	250	66
Aconitic acid	200	<59
Tartaric acid	1400	12
Fumaric acid	11	<9
Sorbic acid	3	<9
Calcium lactate/ Ascorbic acid	50/400	160
Calcium citrate	10	165
Calcium carbonate/ Ascorbic acid	50/400	176
None	--	125

Example 4

The lower solubility of the sertraline chloride salt and of all sertraline lactate and sertraline acetate salts in the presence of high chloride concentrations suggest that core formulations are preferred for which sertraline stays in solution that is, it does not precipitate or form a gel-like material when chloride is present. Certain organic acids and salts were found to inhibit precipitation or gelation of sertaline when chloride is present via the following screening test. Sertraline lactate was dissolved in water either alone (as a control) or with a candidate solubilizing agent. Sodium chloride was then added (as a concentrated solution) and the result observed. An excipient was considered beneficial if the solution remained clear and fluid. The more chloride that could be added to an excipient solution with the solution remaining clear, the more beneficial was the excipient. Table 4-1 below shows the results of this screening test, indicating that all the excipients tested increased sertraline concentration in the chloride solutions.

Table 4-1

Excipient	Excipient Concentration (mg/ml)	Concentration NaCl (mM)	Final Sertraline Concentration (mg/ml)	Observation After NaCl Addition
None	–	38	22	gel/precipitate
Ascorbic/ Aspartic acids	400/7	152	162	solution
Aspartic acid	7 7	114 152	162 100	solution gel
Ascorbic acid	400	100	102	precipitate
Ascorbic acid/ calcium lactate	400/50	150	165	solution
Ascorbic acid/ calcium carbonate	400/50	150	170	slightly turbid
Citric acid/ calcium lactate	600/50	150	162	solution
Histidine	42	150	110	slight precipitate

Example 5

Organic compounds (solubilizers) were screened for their ability to enhance the solubility of sertraline lactate in aqueous solutions with or without the presence of chloride. Excess sertraline lactate was added to an aqueous solution of the candidate solubilizer and, in most cases an organic acid. The organic acids were saturated in these solutions and the additional solubilizing agents were at the concentration shown in Table 5-1. The equilibrium sertraline solubility was measured. Then, sodium chloride was added to the saturated solution and the final sertraline concentration was measured. The results of these screening tests are summarized in Table 5-1.

Table 5-1

	Solubilizer	Solubilizer Concentration (mg/ml)	Organic Acid	Sertraline Solubility (mg/ml)	NaCl Concentration (mM)	Sertraline Concentration with NaCl (mg/ml)
1	None (control)	--	none	125	150	5
2	Monocaprylin	10	ascorbic	160	150	160
3	Triacetin	100	ascorbic	170	150	170
4	Monobutyrin	50	none	120	150	120
5	Diacetin	50	ascorbic	120	150	120
6	Imwitor® 312	10	ascorbic	120	150	120
7	Imwitor® 375	10	ascorbic	120	150	120
8	Imwitor® 742	50	none	120	150	120
9	Imwitor® 988	50	none	140	100	140
10	Triethyl citrate	50	ascorbic	160	150	160
11	Pluronic® L31	50	none	120	100	120
12	Cremophore® EL	50	ascorbic	120	150	120
13	Sucrose acetate isobutyrate	50	ascorbic	120*	150	120
14	Sodium capryl lactate	50	ascorbic	120	150	120
15	Sucrose monolaurate	50	none	150	150	150
16	Sodium lauryl lactate	50	ascorbic	120	150	120
17	Span 80	50	ascorbic	120	150	120

Example 6

This example illustrates that solubilizers for sertraline also can increase the rate of dissolution of sertraline. The effect of a candidate excipient on sertraline dissolution rate was determined by adding solid drug, the candidate solubilizing excipient, and, in some cases, other excipients such as an organic acid and an osmagent (such as a sugar) to a 1.8 ml centrifuge tube. The sample tubes were spun at 14K G for 5 minutes in a microcentrifuge to pack the powder. 150 µl gastric buffer was added to the packed powder and the samples were gently agitated, then spun at 14K G in a microcentrifuge for 2 minutes. The samples were then removed from the microcentrifuge and allowed to stand undisturbed until the solution was removed. The solution was removed from the samples after a total of 10 minutes after gastric buffer was added to the powder pack, and analyzed by HPLC to determine the sertraline concentration.

The dissolution rate (mg sertraline/ml-min) was calculated from the measured concentration of dissolved sertraline in the supernatant as a function of time over the first 10 minutes of dissolution. These dissolution rates and the excipient mixtures for which they were measured are summarized in Table 6-1 below. As shown, several excipient mixtures containing solubilizers significantly (about 3X or greater) increased the dissolution rate of sertraline, compared with sertraline alone and compared with sertraline and ascorbic acid.

Table 6-1

Candidate Excipient		Organic Acid	Organic Acid Conc. (wt%)	Osmagent	Osmagent Conc. (wt%)	Other Excipient	Other Excipient Conc. (wt%)	Sertraline Salt Form Conc. (wt%)	Sertraline Dissolution Rate (mg/ml-min)
Name	Concentration (wt%)								
None	--	none	--	none	--	none	--	lactate 100	
None	--	ascorbic	51.0	lactose	20	none	--	lactate 14	3.5
Imwitor® 312	5.0	ascorbic	49.5	lactose	12.5	$CaCO_3$	5	lactate 14	20.9
Lecithin	5.0	ascorbic	51.0	lactose	15	none	--	lactate 14	10
PEG 3550	5.0	ascorbic	51.0	lactose	15	none	--	lactate 14	9.3
Capmul® MCM	5.0	ascorbic	71.0	none	--	none	--	lactate 24	14.5
Capmul® MCM	4.7	none	none	lactose	17	$CaCO_3$ Ca citrate	4.7 47	lactate 13.1	4.3
Imwitor® 191	5.0	ascorbic	49.5	lactose	12.5	$CaCO_3$	1.0	lactate 14	8.0
Myvrerol® (18-99)	5.0	ascorbic	49.5	lactose	12.5	none	--	lactate 14	6.4
Span® 60	5.0	ascorbic	51.0	lactose	15	none	--	lactate 14	9.5
Ascorbyl palmitate	6.8	none	none	lactose	74.2	none	--	lactate 19	4.3

Methyl paraben/ propyl paraben/ propyl gallate	0.5/0.5/1.0	ascorbic	50.0	lactose	17.5	none	--	lactate 14	11.5
Imwitor® 312	6.8	aspartic	7402	none	--	none	--	lactate 19	5.3

Example 7

This examples illustrates a method for making osmotic tablets comprising a tablet core containing sertraline with and without solubilizing agents surrounded by a semipermeable asymmetric membrane coating. In this example the benefit of incorporating solubilizers into a controlled-release formulation containing sertraline is demonstrated. Sertraline-hydrochloride was triturated by hand for 10 minutes with citric acid and microcrystalline cellulose (Avicel PH 102, FMC) using a 6 1/2 inch diameter mortar and pestle. Magnesium stearate was then blended in as a lubricant by stirring with a spatula for 60 seconds. The weight ratio of sertraline-hydrochloride to citric acid to microcrystalline cellulose to magnesium stearate was 8.5:63.8:23.7:4; with a total weight of 10 grams. The blended mixture was pressed into 470 mg tablets in a modified hydraulic jack (manufactured by Dayton) fitted with a pressure gauge and 3/8 inch concave punch under 2500 PSI pressure for 2 seconds. The dimensions of the resulting tablets were 3/8 inch in diameter and 1/4 inch thick. A semipermeable membrane coating (as described in U.S. Patent 5,612,059 was applied to these tablets using a LDCS-20 pan coater (Vector Corp.) at a spray rate of 20 grams per minute, an inlet temperature of 40°C and air flow of 40 cfm. The coating solution contained by weight 10% Cellulose acetate, (Eastman Chemical, CA398-10), 2.5% polyethylene glycol (BASF, PEG 3350), 15% water and 72.5% acetone. The coated tablets were dried 1 hour at 50°C before testing. After drying, the weight of applied coating material was 15.4% of the total weight. Additional osmotic delivery tablets were prepared by using essentially the same procedure for making the tablet cores and applying the asymmetric membrane coating to the cores described above. The composition of the cores and coating solution varied as shown in Table 7-1. Significant core compositional changes shown include: the sertraline salt form, the type and amount of solubilizer, and the type and amount of osmagent. The amount of binder (Avicel®) lubricant (magnesium stearate), and solubilizer were varied as necessary to obtain good tableting and wetting properties. These tablets all contained a sertraline dose of 50 mgA/tablet.

Table 7-1

Example No.	Core Composition												Coating Solution				
	Core Weight (mg)	Drug		Solubilizer Acid		Solubilizer		Osmogent		Avicel wt %	Mg St. wt %	Other	Polymer Type	Polymer wt %	PEG wt %	Water wt %	Coating Weight (dry wt %)
		Salt Form	Wt %	Type	Wt %	Type	Wt %	Type	Wt %								
7a	470	chloride	12	none		none		lactose	66	20	2	none	CA	10	2.5	15	15.4
7b	470	lactate	14	none		none		lactose	65.4	19.3	1.33	none	EC	6	4	8	1
7c	470	lactate	14	aspartic	11	none		fructose	38	29.5	2.5	Ca Acetate	CA	10	2.5	15	11
7d	470	lactate	14	glutamic	10	MC	5	sucrose	50	15	none	Ca lactate, Myrj	EC	6	4	10	10.1
7e	470	lactate	14	aspartic	11	Im	5	fructose	36	27	2.5	Ca acetate	CA	10	2.5	15	10.3
7f	470	lactate	14	glycine	25	Im	5	fructose	28.5	25	2.5	none	CA	10	2.5	15	15.9
7g	470	lactate	14	aspartic	11	Im	5	fructose	36	27	2.5	Ca acetate	CA	10	2.5	15	20
7h	470	lactate	14	aspartic	11	none		fructose	38	29.5	2.5	Ca acetate	CA	10	2.5	15	10

IM = Imwitor® 312 CA = cellulose acetate 398-10 EC = Ethocel S-100

MC = monocaprylin Mg St. = magnesium stearate

PEG = polyethylene glycol 3350 Myrj = Myrj® 52

The rates of rel ase of sertralin from these formulations were determined testing the tablets in a USP Apparatus #2 with paddle stirring speed set at 100 rpm. The receptor solution used in the dissolution apparatus was 0.13M acetate buffer at pH 4.0 with 0.075M sodium chloride kept at 37°C. Samples of the receptor solution were taken at the times shown in Table 7-2. Analysis of sertraline released was determined by reverse-phase high-performance liquid chromatography (RP HPLC).

The results of release-rate tests performed using these procedures are listed in Table 7-2. The first two formulations listed, 7a and 7b show low release rates and are included as comparison examples. Both these formulations contain a sertraline salt (hydrochloride or lactate) and only lactose as the osmagent and no solubilizing excipients. The remaining formulations (7c-7h) listed in Table 7-2 all contain one or more solubilizing excipients and all demonstrate significantly higher release rates of sertraline compared with the formulations that do not contain solubilizers.

Table 7-2

Tablets of Example No	Fraction of Drug Released (%) At Specified Time						
	0 Hr	1 Hr	2 Hr	4 Hr	8 Hr	12 Hr	20 Hr
7a	0	0	0	0	0	0	0
7b	0	0	1	2	–	10 (17 hr)	12
7c	0	6	15	35	62	76	78
7d	0	0	0	4	19	28	44
7e	0	8	19	37	60	73	83
7f	0	0.7	6	17	37	54	78
7g	0	0.4	4	13	31	41	53
7h	0	8	18	38	56	64	66

What is claimed is:

1. A composition of matter comprising sertraline or a pharmaceutically acceptable salt thereof and an amount of a solubilizing agent sufficient to produce a concentration of dissolved sertraline in a use environment containing chloride ions which is 1.5 times higher than the concentration effected by a comparative composition of matter identical thereto but for the inclusion of said solubilizing agent.

2. A composition of matter as defined in claim 1, wherein said use environment is the GI tract.

3. A composition of matter as defined in claim 1, wherein said use environment is an aqueous chloride ion-containing test medium.

4. A composition of matter as defined in claim 3, wherein said use environment is 0.075 M sodium chloride.

5. A composition of matter as defined in claim 1, which is an immediate release dosage form.

6. A composition of matter as defined in claim 1, which is a controlled release dosage form.

7. A composition of matter as defined in claim 1, wherein said solubilizing agent is selected from:

1) organic acids and organic acid salts;
2) partial glycerides;
3) glycerides;
4) glyceride derivatives;
5) polyethylene glycol esters;
6) polypropylene glycol esters;
7) polyhydric alcohol esters;

8) polyoxyethylene eth rs;

9) sorbitan esters;

10) polyoxyethylene sorbitan esters; and

11) carbonate salts.

8. A composition of matter as defined in claim 4, wherein the amount of said solubilizing agent is sufficient to maintain, for at least 2 hours, the concentration of dissolved sertraline at a level which is at least 1.5 times higher than the concentration of sertraline produced by a comparative composition of matter identical thereto but for the inclusion of said solubilizing agent.

9. A composition as defined in claim 1, wherein said solubilizing agent is selected from aspartic acid, glyceryl monocaprylate, glyceryl monolaurate, calcium acetate, ascorbic acid, citric acid, glutamic acid, and calcium carbonate.

10. A composition of matter comprising sertraline or a pharmaceutically acceptable salt thereof and an amount of a solubilizing agent sufficient to produce and to maintain, for at least 2 hours in 0.075M sodium chloride, a concentration of dissolved sertraline which is at least 1.5 times higher than the concentration effected by a comparative composition of matter identical thereto but for the inclusion of said solubilizing agent.

11. A composition of matter as defined in claim 10, which is an immediate release dosage form.

12. A composition of matter as defined in claim 10, which is a controlled release dosage form.

13. A composition of matter as defined in claim 10, wherein said solubilizing agent is selected from:

1) organic acids and organic acid salts;

2) partial glycerides;

3) glycerid s;
4) glyceride derivatives;
5) polyethylene glycol esters;
6) polypropylene glycol esters;
7) polyhydric alcohol esters;
8) polyoxyethylene ethers;
9) sorbitan esters;
10) polyoxyethylene sorbitan esters; and
11) carbonate salts.

14. A composition as defined in claim 10, wherein said solubilizing agent is selected from aspartic acid, glyceryl monocaprylate, glyceryl monolaurate, calcium acetate, ascorbic acid, citric acid, glutamic acid, and calcium carbonate.

15. A composition of matter comprising sertraline or a pharmaceutically acceptable salt thereof and an amount of a solubilizing agent sufficient to effect, *in vivo*, a C_{max} and/or an AUC which is greater by at least 10% than the C_{max} and/or AUC effected by a comparative composition of matter identical thereto but for the inclusion of said solubilizing agent.

16. A composition as defined in claim 15, wherein said C_{max} and/or AUC effected by said solubilizing agent-containing composition is at least 15% higher than the corresponding C_{max} and/or AUC effected by said comparative composition.

17. A composition as defined in claim 16, wherein said C_{max} and/or AUC effected by said solubilizing agent-containing composition is at least 20% higher than the corresponding C_{max} and/or AUC effected by said comparative composition.

18. A composition of matter as defined in claim 15, which is an immediate release dosage form.

19. A composition of matter as defined in claim 15, which is a controlled release dosage form.

20. A composition of matter as defined in claim 15, wherein said solubilizing agent is selected from:

1) organic acids and organic acid salts;
2) partial glycerides;
3) glycerides;
4) glyceride derivatives;
5) polyethylene glycol esters;
6) polypropylene glycol esters;
7) polyhydric alcohol esters;
8) polyoxyethylene ethers;
9) sorbitan esters;
10) polyoxyethylene sorbitan esters;
11) carbonate salts.

21. A composition of matter as defined in claim 15, wherein said solubilizing, agent is selected from aspartic acid, glyceryl monocaprylate, glyceryl monolaurate, calcium acetate, ascorbic acid, citric acid, glutamic acid, and calcium carbonate.

22. A method of increasing the solubility of sertraline in an aqueous chloride ion-containing use environment, comprising administering said sertraline to said use environment in a composition of matter additionally comprising a solubilizing agent.

23. A method as defined in claim 22, wherein the concentration of dissolved sertraline in said use environment also containing said solubilizer is at least 1.5-fold higher than the concentration of sertraline effected by a comparative composition identical to said solubilizing agent-containing composition except for the inclusion of said solubilizing agent.

24. A method as defined in claim 22, wherein said use environment is the GI tract.

25. A method as defined in claim 22, wherein said use environment is an aqueous chloride ion-containing test medium.

26. A method as defined in claim 25, wherein said medium is 0.075 M sodium chloride.

27. A method as defined in claim 22, wherein said composition of matter is in the form of an immediate release dosage form.

28. A method as defined in claim 22, wherein said composition of matter is in the form of a controlled release dosage form.

29. A method as defined in claim 22, wherein said solubilizing agent is selected from:

1) organic acids and organic acid salts;
2) partial glycerides;
3) glycerides;
4) glyceride derivatives;
5) polyethylene glycol esters;
6) polypropylene glycol esters;
7) polyhydric alcohol esters;
8) polyoxyethylene ethers;
9) sorbitan esters; and
10) polyoxyethylene sorbitan esters.
11) carbonate salts